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June 13, 2003

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June 13, 2003 — Date
Michael C. Barrett — Michael C. Barrett

MAIL STOP AF
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

RE: *SN 09/748,133 "pH-SENSITIVE MUCOADHESIVE FILM-FORMING GELS AND WAX-FILM COMPOSITES SUITABLE FOR TOPICAL AND MUCOSAL DELIVERY OF MOLECULES" - Mumper et al*

Commissioner:

Transmitted herewith for filing are:

1. An Appeal Brief **(an original and two copies)**;
2. A check for $160.00 to cover the filing fee(s); and
3. A return postcard to acknowledge receipt of these materials. Please date stamp and mail this postcard.

If the check is inadvertently omitted, or the amount is insufficient, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski L.L.P. Account No.: 50-1212/NANO:002US/MCB.

Respectfully submitted,

Michael C. Barrett
Reg. No. 44,523

MCB/lak
Enclosures

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June 13, 2003 — Michael C. Barrett
Date — Michael C. Barrett

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Mumper *et al.*

Serial No.: 09/748,133

Filed: December 27, 2000

For: pH-Sensitive Mucoadhesive Film-Forming Gels and Wax-Film Composites Suitable for Topical and Mucosal Delivery of Molecules

Group Art Unit: 3309

Examiner: Robert M. DeWitty

Atty. Dkt. No.: NANO:002US/MCB

APPEAL BRIEF

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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APPEAL BRIEF

BOX AF
Commissioner of Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences in response to the final Office Action dated December 18, 2002 and the Advisory Action dated March 21, 2003. The Notice of Appeal was received by the Patent Office on April 14, 2003, as indicated by a stamped postcard. This Appeal Brief is timely filed because the due-date is June 16, 2003. The filing fee of $160.00 is included.

Applicant believes that no additional fees are due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct those fees from Fulbright & Jaworski Deposit Account No. 50-1212/NANO:002US/MCB. If overpayment is included, the Commissioner is authorized to credit that account.

Please date stamp and return the attached postcard as evidence of receipt.

I. REAL PARTY IN INTEREST

The real party in interest is the assignee, University of Kentucky Research Foundation.

II. RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are presently pending.

III. STATUS OF THE CLAIMS

Claims 1–62 were originally filed on December 27, 2000. In response to a restriction requirement mailed on November 16, 2001, Applicant elected to pursue claims 1–32. In response to the first Office Action mailed on May 8, 2002, claims 1, 4, 8, 19, and 23 were amended. In response to the Final Office Action mailed December 18, 2002, claims 1-15 were amended to add material from the preamble into the body. However, in an Advisory Action mailed March 21, 2003, those preamble-related amendments were refused entry because they allegedly raised new matter, would require a new search/consideration, and/or did not place the application in better condition for allowance or appeal.[1]

IV. STATUS OF AMENDMENTS

No amendments are being filed with this Appeal Brief. Therefore, the claims are in the same condition as they were following the response to first Office Action.

V. SUMMARY OF THE INVENTION

The invention generally concerns a gel that forms a film upon application to the skin or a mucosal surface and that can deliver a drug or other substance.[2] *See* specification, p.1, Field of Invention. The gel, in one embodiment, includes a solvent vehicle. *See* specification, p. 5, ¶1 of

[1] Applicant respectfully submits that it was improper for the Office to refuse entry of such amendments, does not acquiesce in the Office's justification for refusing entry, and reserves the right to traverse the Office's justification, if necessary.

[2] The claims of the invention are not limited by this summary—the embodiments listed in the summary are exemplary only. Recitation of support in the specification does not imply that is the *only* support that may be found.

Summary of the Invention. It also includes a water-insoluble swellable mucoadhesive polymer, a pH-sensitive film-forming polymer, and a molecule of interest. *Id.* The pH-sensitive film-forming polymer forms a film when applied to skin or a mucosal surface. *Id.*

The solvent vehicle can include at least 25 to 100 parts water or buffered water with 0 to 75 parts of ethanol, propylene glycol, glycerin, polyethylene glycol, or combinations thereof. *Id.* at ¶2 of Summary of the Invention.

The water-insoluble swellable mucoadhesive polymer can be polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol. *Id.* Alternatively, the water-insoluble swellable mucoadhesive polymer can be NOVEON or CARBOMER. *Id.* The water-insoluble swellable mucoadhesive polymer can be present at a concentration of from 0.1% to 20% by weight. *Id.*

The pH-sensitive polymer can be a copolymer of methacrylic acid and acrylic or methacrylic ester. *Id.* at ¶3 of Summary of the Invention. The pH-sensitive polymer can be present at a concentration of from 0.05% to 10% by weight. *Id.* The pH-sensitive polymer can be a EUDRAGIT polymer, or a chemical derivative thereof. *Id.*

The molecule of interest can include an active pharmaceutical such as an antimicrobial, antiviral, antiinflammatory, antiseptic, antihistamine, a local anesthetic, a disinfectant, a keratolytic, an analgesic, an anti-migraine, an anti-fungal, a sweetener, a flavoring agent, a diagnostic agent, or combination thereof. *See* specification, p. 6, ¶1. The molecule of interest can be:

- amlexanox.
- triclosan.
- peptide or protein
- hirudin.

- plasmid DNA.
- lidocaine, benzocaine, or dyclonine.
- at least one benzodiazepine drug or derivative thereof.

Id.

In another embodiment, the invention concerns a pharmaceutical gel which, when applied to the skin or mucosal surface, forms a film. *Id.* at ¶2. The gel includes a solvent vehicle, at least one water-insoluble swellable mucoadhesive polymer, at least one pH-sensitive film-forming polymer, and at least one molecule of interest. *Id.* The film is formed due to changes in pH and desolvation of the polymer, and the film provides for the delivery of the molecule of interest to or through the application site. *Id.*

The application site can be the skin, mouth, vagina, nose, nasal cavity, or other accessible mucosal site. *Id.* at ¶4.

VI. ISSUES ON APPEAL

The following issue is presented for review:

(1) whether the pending claims are obvious under 35 U.S.C. § 103 in view of Vora, Acharya, and Benes.

VII. GROUPING OF THE CLAIMS

Each claim stands on its own.

VIII. ARGUMENT

A. Substantial evidence is required to uphold the Examiner's position

As an initial matter, Applicant notes that findings of fact and conclusions of law by the U.S. Patent and Trademark Office must be made in accordance with the Administrative Procedure Act, 5 U.S.C. § 706(A), (E), 1994. *Dickinson v. Zurko*, 527 U.S. 150, 158 (1999).

Moreover, the Federal Circuit has held that findings of fact by the Board of Patent Appeals and Interferences must be supported by "substantial evidence" within the record. *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). In *Gartside*, the Federal Circuit stated that "the 'substantial evidence' standard asks whether a reasonable fact finder could have arrived at the agency's decision." *Id.* at 1312.

Accordingly, an Examiner's position on Appeal must be supported by "substantial evidence" within the record in order to be upheld by the Board of Patent Appeals and Interferences.

B. The cited references do not, and cannot, support a *prima facie* case of obviousness

All the pending claims have been rejected as obvious based on the three-way combination of (1) Vora, (2) Acharya, and (3) Benes. The Office has not established a *prima facie* case of obviousness, and all the rejections should be withdrawn.

Three basic criteria must be met to establish a *prima facie* case of obviousness:

(1) the prior art reference (or references when combined) must teach or suggest all the claim limitations;

(2) there must be some suggestion or motivation, either in the References themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; and

(3) there must be a reasonable expectation of success.

See M.P.E.P. § 2142.

Here, the Office has not established a *prima facie* case, for it has not established *any* of these three prongs.

1. The references, even when combined, do not teach or suggest all the claim limitations

Even if the three cited references were combined, all of the present claim limitations would not be taught or even suggested.

a) Claim 1 is not taught or suggested by the references

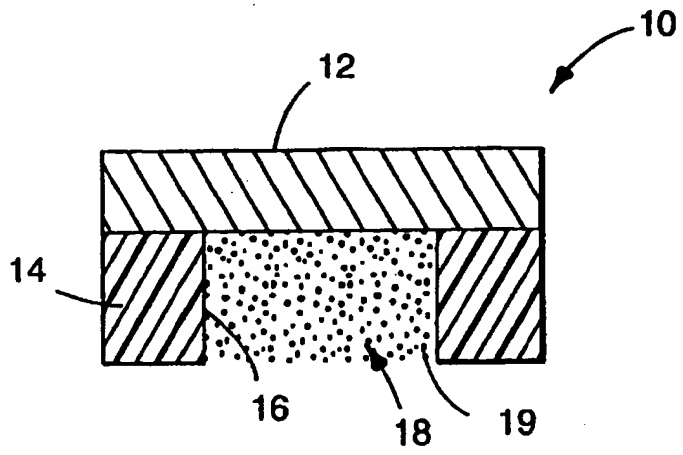
Independent claim 1 recites, in part, "A pharmaceutical gel composition comprising ... at least one pH-sensitive film-forming polymer *forming a film when applied to skin or a mucosal surface* ... ." Such features are nowhere taught or suggested in the cited art, taken alone or in any combination.

Vora is directed to a method to treat aphthous ulcers using a paste, solution, gel, and other conventional formulations. *See* col. 2, lines 42-47. In contrast to the present invention, Vora nowhere discloses or suggests the use of a pharmaceutical gel utilizing a pH-sensitive film-forming polymer that, when applied to the skin or mucosal surface, forms a film. The Office has pointed to no passage or figure to suggest otherwise.

Acharya is directed to the use of calcium polycarbophil gels to deliver active agents. Abstract. Acharya discloses the formation of a polymeric complex carrier formed by the interaction of calcium and polycarbophil. Col. 3, lines 15-25. Specifically, Acharya discloses that the composition is supplied as a two-part system, a polymer phase and a liquid phase. Col. 3 lines 33-39. Acharya nowhere discloses or suggests the use of a pharmaceutical gel utilizing a pH-sensitive film-forming polymer that, when applied to the skin or mucosal surface, forms a film. The Office has pointed to no passage or figure to suggest otherwise.

Benes is directed to the use of a *device* for the delivery a heparinic anticoagulant across a mucosal surface. Abstract. The device includes a reservoir containing a matrix (*i.e.*, a gel, powder, or tablet containing a heparinic anticoagulant) and an outer mucoadhesive portion.

Figure 1. The outer mucoadhesive portion is a pre-formed solvent-casted film combination of a polymeric resin (i.e., CARBOPOL) with an elastomeric component. Col. 5, lines 24-36. Benes discloses the use of basic (cationic) polyamines such as EUDRAGIT E only to "neutralize" this resin. Col. 6 lines 13-17. As evidenced by Figure 1 of Benes, this pre-formed outer mucoadhesive coating is a pre-casted film (or "sheet") that is subsequently filled with a gel containing a heparinic anticoagulant. *See* Example 1; *see also* col. 9 lines 30-67. In Figure 1 of Benes, reproduced below, element 10 refers to the device, element 12 is a backing layer, element 14 is a layer of mucoadhesive, element 16 is a reservoir, element 18 is a matrix, and element 19 is a heparinic anticoagulant. *See* col. 6, line 65 - col. 7, line 3.



Importantly, Benes nowhere teaches a pharmaceutical gel including a pH-sensitive film-forming polymer that, when applied to the skin or mucosal surface, forms a film. Specifically, the disclosure of a gel (*e.g.* element 18 above) residing within a reservoir (*e.g.*, element 16 above) defined by a pre-formed, neutralized film coating (*e.g.*, element 14 above) does *not* amount to the disclosure or even suggestion of a gel composition including a component that, upon application to the skin or mucosal surface, itself forms a film. In fact, it can be argued that the disclosure of Benes *teaches away* from such a concept because it effectively teaches the

advantages of using a pre-formed film or sheet with a backing to create a gel-filled reservoir. *See* Figure 1 (above).

The Office's present arguments appear to be an improper piecing-together of disparate elements from different references. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 416 (Fed. Cir. 1986) ("It is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art."). For example, the Office argues that the film-forming component of the presently-recited gel is contained in Benes, when in fact, Benes simply mentions that EUDRAGIT can be used to neutralize a resin within a pre-formed sheet (*see* element 14 in the reproduced figure above). Col. 6, lines 13-17; Figure 1. The mere naming of EUDRAGIT in the Benes reference (in a different context) does not establish the claimed elements, nor does it advance any basis for obviousness under an "inherency" theory. *In re Newell*, 13 U.S.P.Q.2d 1248 (Fed. Cir. 1989) ("*[A] retrospective view of inherency is not a substitute for some teaching or suggestion* which supports the selection and use of the various elements in the particular claimed combination.") (emphasis added).

Accordingly, *none* of the cited teaches or even suggests the elements required by pending claim 1—particularly, a gel utilizing a pH-sensitive film-forming polymer that forms a film when applied to skin or a mucosal surface. Thus, even if the references are combined, an explicit limitation of claim 1 is glaringly absent from the combination of references. Notably, the Office has not been able to point to a single passage of any of the references that would teach or suggest such a gel as required by claim 1, and the Board is invited to look at the record for confirmation.

Thus, there can be no *prima facie* case of obviousness; claim 1 is accordingly in condition for allowance, and the rejection should be withdrawn.

b) Claim 16 is not taught or suggested by the references

Independent claim 16 recites, in part, "A *pharmaceutical gel which when applied to the skin or mucosal surface forms a film,* said gel comprising ... at least one pH-sensitive film-forming polymer ... wherein *said film is formed due to changes in pH and desolvation of the polymer, and wherein said film provides for the delivery of the molecule of interest to or through the application site....*" (emphasis added). Such features are nowhere taught or suggested in the cited art, taken alone or in any combination.

The references, even when combined, do not teach or suggest a pharmaceutical gel which when applied to the skin or mucosal surface forms a film for the reasons given above with respect to claim 1. Moreover, the references, even when combined, do not teach or suggest such a gel film that is formed due to changes in pH and desolvation of the polymer as required by claim 16. The Office has pointed to no passage of any of the references to suggest otherwise.

Moreover, claim 16 requires that the polymer-formed film (formed due to changes in pH and desolvation of the polymer) provide for the delivery of a molecule of interest to or though an application site. Here too, the references, even when combined, do not teach or suggest such a gel, and the Office has pointed to no passage of any of the references to suggest otherwise.

Thus, in view of at least these independent reasons, there can be no *prima facie* case of obviousness; claim 16 is accordingly in condition for allowance, and the rejection should be withdrawn.

c) Claims 2–15 and 17–32 are not taught or suggested by the references

Dependent claims 2–15 and 17–32 include several requirements above and beyond their independent claims. It appears that the Office has focused its attention on the independent claims, and it has correspondingly not provided evidence why these dependent claims are not patentable. In particular, the Office has not pointed to passages or figures in the cited art to show that these features are taught or even suggested. Thus, no *prima facie* case of obviousness has been established with respect to any of the dependent claims, and the rejections should be withdrawn.

For instance, claim 2 requires (in addition to the elements of claim 1):

- the solvent vehicle is comprised of at least 25 to 100 parts water or buffered water with 0 to 75 parts of ethanol, propylene glycol, glycerin, polyethylene glycol, or combinations thereof

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 3 requires (in addition to the elements of claim 1):

- the water-insoluble swellable mucoadhesive polymer is polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 4 requires (in addition to the elements of claim 1):

- the water-insoluble swellable mucoadhesive polymer is NOVEON or CARBOMER.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 5 requires (in addition to the elements of claim 1):

- the water-insoluble swellable mucoadhesive polymer is present at a concentration of from 0.1% to 20% by weight.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 6 requires (in addition to the elements of claim 1):

- the pH-sensitive polymer is a copolymer of methacrylic acid and acrylic or methacrylic ester.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 7 requires (in addition to the elements of claim 1):

- the pH-sensitive polymer is present at a concentration of from 0.05% to 10% by weight.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 8 requires (in addition to the elements of claim 1):

- the pH-sensitive polymer is a EUDRAGIT polymer, or a chemical derivative thereof.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 9 requires (in addition to the elements of claim 1):

- the molecule of interest comprises an active pharmaceutical such as an antimicrobial, antiviral, antiinflammatory, antiseptic, antihistamine, a local anesthetic, a disinfectant, a keratolytic, an analgesic, an anti-migraine, an anti-fungal, a sweetener, a flavoring agent, a diagnostic agent, or combination thereof.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 10 requires (in addition to the elements of claim 1):

- the molecule of interest is amlexanox.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 11 requires (in addition to the elements of claim 1):

- the molecule of interest is triclosan.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 12 requires (in addition to the elements of claim 1):

- the molecule of interest is hirudin.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 13 requires (in addition to the elements of claim 1):

- the molecule of interest is plasmid DNA.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 14 requires (in addition to the elements of claim 1):

- the molecule of interest is lidocaine, benzocaine, or dyclonine.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 15 requires (in addition to the elements of claim 1):

- the molecule of interest is at least one benzodiazepine drug or derivative thereof.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 17 requires (in addition to the elements of claim 16):

- the solvent vehicle is comprised of at least 25 to 100 parts water with 0 to 75 parts of ethanol, propylene glycol, glycerin, polyethylene glycol, or combinations thereof.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 18 requires (in addition to the elements of claim 16):

- the water-insoluble swellable mucoadhesive polymer is polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 19 requires (in addition to the elements of claim 16):

- the water-insoluble swellable mucoadhesive polymer is NOVEON or CARBOMER.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 20 requires (in addition to the elements of claim 16):

- the water-insoluble swellable mucoadhesive polymer is present at a concentration of from 0.1% to 20% by weight.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 21 requires (in addition to the elements of claim 16):

- the pH-sensitive polymer is a copolymer of methacrylic acid and acrylic or methacrylic ester.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 22 requires (in addition to the elements of claim 16):

- the pH-sensitive polymer is present at a concentration of from 0.05% to 10% by weight.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 23 requires (in addition to the elements of claim 16):

- the pH-sensitive polymer is a EUDRAGIT polymer, or chemical derivative thereof.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 24 requires (in addition to the elements of claim 16):

- the molecule of interest comprises an active pharmaceutical such as an antimicrobial, antiviral, antiinflammatory, antiseptic, antihistamine, a local anesthetic, a disinfectant, a keratolytic, an analgesic, an anti-migraine, an anti-fungal, a sweetener, a flavoring agent, a diagnostic agent, or combination thereof.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 25 requires (in addition to the elements of claim 16):

- the molecule of interest is amlexanox.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 26 requires (in addition to the elements of claim 16):

- the molecule of interest is triclosan.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 27 requires (in addition to the elements of claim 16):

- the molecule of interest is a peptide or protein.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 28 requires (in addition to the elements of claim 16):

- the molecule of interest is hirudin.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 29 requires (in addition to the elements of claim 16):

- the molecule of interest is plasmid DNA.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 30 requires (in addition to the elements of claim 16):

- the molecule of interest is lidocaine, benzocaine, or dyclonine.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 31 requires (in addition to the elements of claim 16):

- the molecule of interest is at least one benzodiazepine drug or derivative thereof.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

Claim 32 requires (in addition to the elements of claim 16):

- the application site is the skin, mouth, vagina, nose, nasal cavity, or other accessible mucosal site.

The Office has not provided evidence to show or suggest that this claim is not patentable; accordingly, no *prima facie* case has been established.

2. There is no suggestion or motivation to modify the references or to combine the reference teachings with respect to any of the pending claims

In order for the cited references to even arguably be pertinent, one of ordinary skill in the art would have to significantly modify Benes, which discloses that EUDRAGIT is used simply to neutralize a pre-formed outer film layer that encases a reservoir of gel. Col. 6 , lines 13-17; Figure 1, above. In particular, Benes would have to be modified so that the EUDRAGIT, instead of simply neutralizing the pre-formed outer coating, would instead be appropriately combined in a particular gel composition in such a way (not disclosed or suggested) that a film would form upon application to the skin or mucosal surface. *See, e.g.*, independent claims 1, 16. No motivation exists (or is cited by the Office) for this modification. Further, such a modification would change the operation of Benes—instead of utilizing the pre-formed film encasing the reservoir, Benes would operate by utilizing a gel that *itself* formed a film upon application. Accordingly, this modification is clearly improper. *See* M.P.E.P. 2143.01 ("If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious."). All the pending claims are therefore in condition for allowance, and the rejections should be withdrawn because no *prima facie* case has been established.

3. The Office has not established that there would be a reasonable expectation of success with respect to any of the pending claims

The Office has not shown or argued the required reasonable expectation of success. Applicants respectively submit that there is *nothing* in the cited art that demonstrates a reasonable expectation of success surrounding the significant modification of Benes discussed above. In particular, there is nothing in the record to suggest that the abandonment of the pre-formed film encasing a gel in Benes in favor of a different gel composition (not disclosed) including a film-forming polymer that forms a suitable film upon application to the skin or mucosal surface would be successful. Accordingly, for this reason as well, the pending claims are not *prima facie* obvious and the rejections should be withdrawn.

C. The Office's rebuttal to Applicant's arguments do not establish or bolster any *prima facie* case of obviousness

a) Final Office Action rebuttal

In the Office's Final Office Action mailed December 18, 2002, a "Response to Arguments" section is included. There, the Office argues that:

1) Vora teaches using a gel;
2) Acharya teaches films being used to contact mucosal or skin surfaces;
3) Benes teaches the administration of drugs across mucosal surfaces.

The Examiner concludes that the art therefore meets the limitations of claim 1. Applicant traverses. The references clearly lack disclosure or suggestion of the particular gel of claim 1: a pharmaceutical gel having at least one pH-sensitive film-forming polymer forming a film when applied to skin or a mucosal surface. Likewise, the gel of claim 16 is not disclosed or suggested. *Separate* recitations of films, drugs, and gels do not amount to the disclosure or suggestion of such a particular gel. In fact, combining references despite any motivation amounts to impermissible hindsight. *See Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5 (Fed. Cir.

1986) (noting that references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention). And, the fact that the references *can* be combined or modified is not sufficient to establish *prima facie* obviousness. *See In re Mills*, 916 F.2d 680 (Fed. Cir. 1990); M.P.E.P. § 2143.01.

Despite the Examiner's assertion otherwise, Applicant has not improperly attacked references individually. Again, *none* of the references disclose or suggest such a gel, and the Office has been able to point to any passage or figure in any reference to suggest otherwise. Thus, even in combination, a *prima facie* case for obviousness has not been met.

In the second paragraph of the "Response to Arguments" section, the Office argues that:

1) Benes does not need to be modified to meet the claims;
2) Benes teaches a matrix, which can be a gel;
3) Benes teaches means for maintaining the matrix in contact with a mucosal surface;
4) The means include resins containing coboxylic acid moieties; and
5) Benes meets the claims because it is "drawn to a gel-formed delivery device that can consist of Eudragit."

Applicant again traverses. The Office's position is that any "gel-formed delivery device that can consist of Eudragit" renders the claims obvious. This is in error. The claims are not that broad, nor do they purport to be. Claim 1 recites a gel that includes at least one pH-sensitive film-forming polymer forming a film when applied to skin or a mucosal surface. Claim 16 is similar and includes even further reasons for patentability (see arguments above). Disclosure of a pre-formed outer mucoadhesive coating that is subsequently filled with a separate gel, as done in Benes, simply does not amount to a disclosure or even a teaching of such a gel. Benes would have to be significantly modified to change the composition of its gel "matrix" so that such gel would include additional materials to ensure that a film be formed when applied to skin or a

mucosal surface. Motivation for that modification is lacking, and the Office has pointed to no evidence to support a *prima facie* case.

In the third paragraph of the "Response to Arguments" section, the Office argues that Benes requires no modification. Applicant traverses. Again, Benes would have to be changed so that its gel would be different to ensure that it would form a film when applied to the skin or mucosal surface. The Office has not shown why such a modification would have a reasonable expectation of success nor has it pointed to any evidence from the references.

While Applicant appreciates the Office's explanation of rejections, the reasoning and assertions given in support thereof are traversed. The cited references do not disclose or suggest, alone or in combination, the features of the pending claims. The claims are in condition for allowance, and a withdrawal of the rejections is respectfully requested.

b) Advisory Action rebuttal

In the Office's Advisory Action mailed March 21, 2003, the Office implies that Applicant's claims are limited (or intended to be limited) to a particular type of EUDRAGIT. Applicant traverses. In a telephone interview with the Examiner, Applicant suggested, in an attempt to avoid the need for the present appeal, the possibility of amending certain claims to recite a particular preferred EUDRAGIT.[3] However, such an amendment was not pursued and is not necessary because the claims are already clearly patentable for the reasons given here. Any implication that claims not mentioning EUDRAGIT are nevertheless so-limited is traversed.

In the Advisory Action, the Office also appears to argue that it is ignoring express limitations of the pending claims. The Office states:

[3] The specification discloses that anionic EUDRAGIT is preferred, but not required. *See* paragraphs spanning pp. 16–17. Applicant briefly considered amending certain claims to require the preferred anionic form of EUDRAGIT but ultimately decided that such an amendment was not warranted given that the claims are patentable as-written.

> Further, the claims are drawn to a composition as it would exist prior to application to the skin and the mucoadhesive of Benes meet these limitations. While Benes may not recognize that the composition may be applied directly to the skin in liquid form, this failure does not render the composition patentably distinct.

The Office appears to ignore that the claims are directed to a gel including particular components, one of which is a particular pH-sensitive film-forming polymer. Benes and the other cited art admittedly do not include a gel having such a pH-sensitive film-forming polymer. The Office's statement that the claims are drawn to a composition *prior to application* is misplaced—even prior to application, the claims require the gel to include a particular pH-sensitive film-forming polymer, which is absent from the prior art. Accordingly, the Office's rebuttal in the Advisory Action fails to establish a *prima facie* case of obviousness, and the rejections should be withdrawn.

IX. APPENDIX

The pending claims are provided in Appendix A.

X. CONCLUSION

Applicant has provided arguments that overcome all the pending rejections. Applicant respectfully submits that the Office Action's conclusions that the claims should be rejected are unwarranted. It is therefore requested that the Board overturn the rejections.

Please date stamp and return the enclosed postcard to evidence receipt of this document.

Respectfully submitted,

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Appendix A: Pending Claims

1. A pharmaceutical gel composition comprising:

    a solvent vehicle,

    at least one water-insoluble swellable mucoadhesive polymer,

    at least one pH-sensitive film-forming polymer forming a film when applied to skin or a mucosal surface, and

    at least one molecule of interest.

2. The gel of claim 1, wherein the solvent vehicle is comprised of at least 25 to 100 parts water or buffered water with 0 to 75 parts of ethanol, propylene glycol, glycerin, polyethylene glycol, or combinations thereof.

3. The gel of claim 1, wherein the water-insoluble swellable mucoadhesive polymer is polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol.

4. The gel of claim 1, wherein the water-insoluble swellable mucoadhesive polymer is NOVEON or CARBOMER.

5. The gel of claim 1, wherein the water-insoluble swellable mucoadhesive polymer is present at a concentration of from 0.1% to 20% by weight.

6. The gel of claim 1, wherein the pH-sensitive polymer is a copolymer of methacrylic acid and acrylic or methacrylic ester.

7. The gel of claim 1, wherein the pH-sensitive polymer is present at a concentration of from 0.05% to 10% by weight.

8. The gel of claim 1, wherein the pH-sensitive polymer is a EUDRAGIT polymer, or a chemical derivative thereof.

9. The gel of claim 1, wherein the molecule of interest comprises an active pharmaceutical such as an antimicrobial, antiviral, antiinflammatory, antiseptic, antihistamine, a local anesthetic, a disinfectant, a keratolytic, an analgesic, an anti-migraine, an anti-fungal, a sweetener, a flavoring agent, a diagnostic agent, or combination thereof.

10. The gel of claim 1, wherein the molecule of interest is amlexanox.

11. The gel of claim 1, wherein the molecule of interest is triclosan.

12. The gel of claim 1, wherein the molecule of interest is hirudin.

13. The gel of claim 1, wherein the molecule of interest is plasmid DNA.

14. The gel of claim 1, wherein the molecule of interest is lidocaine, benzocaine, or dyclonine.

15. The gel of claim 1, wherein the molecule of interest is at least one benzodiazepine drug or derivative thereof.

16. A pharmaceutical gel which when applied to the skin or mucosal surface forms a film, said gel comprising a solvent vehicle, at least one water-insoluble swellable mucoadhesive polymer, at least one pH-sensitive film-forming polymer, and at least one molecule of interest, wherein said film is formed due to changes in pH and desolvation of the polymer, and wherein said film provides for the delivery of the molecule of interest to or through the application site.

17. The gel of claim 16, wherein the solvent vehicle is comprised of at least 25 to 100 parts water with 0 to 75 parts of ethanol, propylene glycol, glycerin, polyethylene glycol, or combinations thereof.

18. The gel of claim 16, wherein the water-insoluble swellable mucoadhesive polymer is polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol.

19. The gel of claim 16, wherein the water-insoluble swellable mucoadhesive polymer is NOVEON or CARBOMER.

20. The gel of claim 16, wherein the water-insoluble swellable mucoadhesive polymer is present at a concentration of from 0.1% to 20% by weight.

21. The gel of claim 16, wherein the pH-sensitive polymer is a copolymer of methacrylic acid and acrylic or methacrylic ester.

22. The gel of claim 16, wherein the pH-sensitive polymer is present at a concentration of from 0.05% to 10% by weight.

23. The gel of claim 16, wherein the pH-sensitive polymer is a EUDRAGIT polymer, or chemical derivative thereof.

24. The gel of claim 16, wherein the molecule of interest comprises an active pharmaceutical such as an antimicrobial, antiviral, antiinflammatory, antiseptic, antihistamine, a local anesthetic, a disinfectant, a keratolytic, an analgesic, an anti-migraine, an anti-fungal, a sweetener, a flavoring agent, a diagnostic agent, or combination thereof.

25. The gel of claim 16, wherein the molecule of interest is amlexanox.

26. The gel of claim 16, wherein the molecule of interest is triclosan.

27. The gel of claim 16, wherein the molecule of interest is a peptide or protein.

28. The gel of claim 16, wherein the molecule of interest is hirudin.

29. The gel of claim 16, wherein the molecule of interest is plasmid DNA.

30. The gel of claim 16, wherein the molecule of interest is lidocaine, benzocaine, or dyclonine.

31. The gel of claim 16, wherein the molecule of interest is at least one benzodiazepine drug or derivative thereof.

32. The gel of claim 16, wherein the application site is the skin, mouth, vagina, nose, nasal cavity, or other accessible mucosal site.